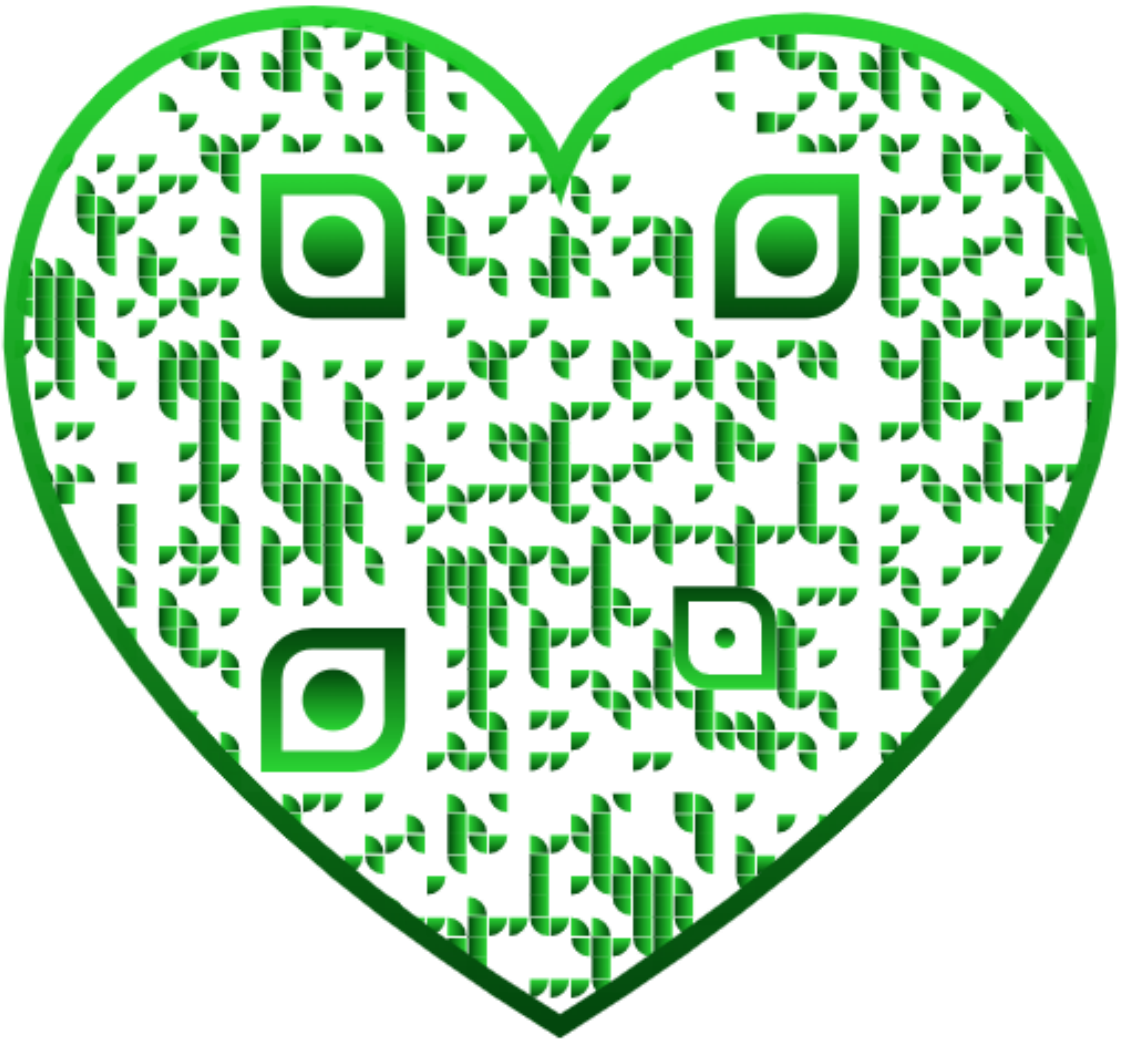
2.7 PK of Extravascular Administration



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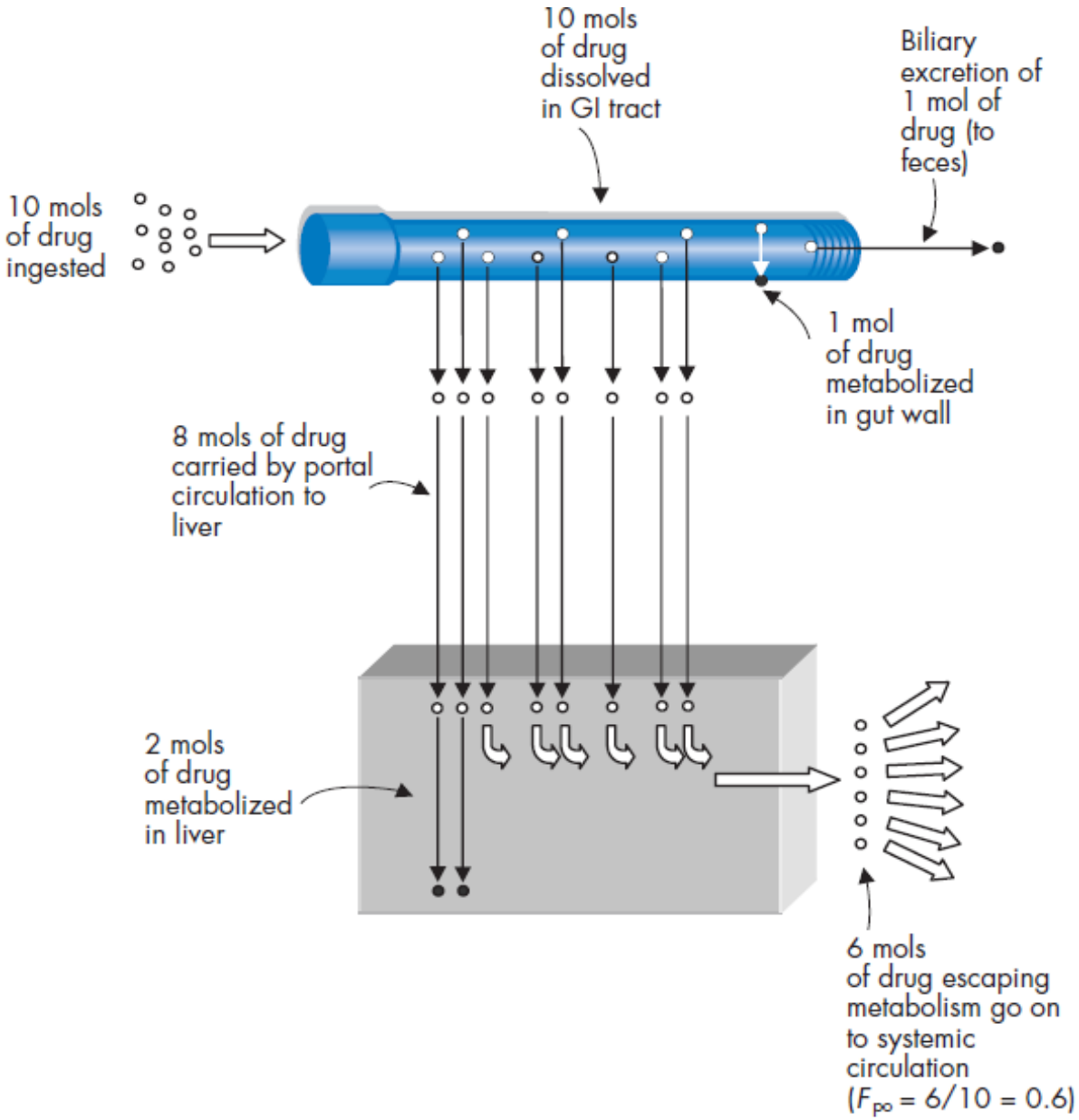
- For extravascular administration, absorption is a prerequisite for pharmacological effects.

- Delays or drug loss during absorption may contribute to variability in drug response and, occasionally, may result in a failure of drug therapy.


10 mols of drug dissolved in GI tract
Biliary excretion of 1 mol of drug (to feces)
10 mols of drug ingested
1 mol of drug metabolized in gut wall
8 mols of drug carried by portal circulation to liver
2 mols of drug metabolized in liver
6 mols of drug escaping metabolism go on to systemic circulation (F_{po} = 6/10 = 0.6)

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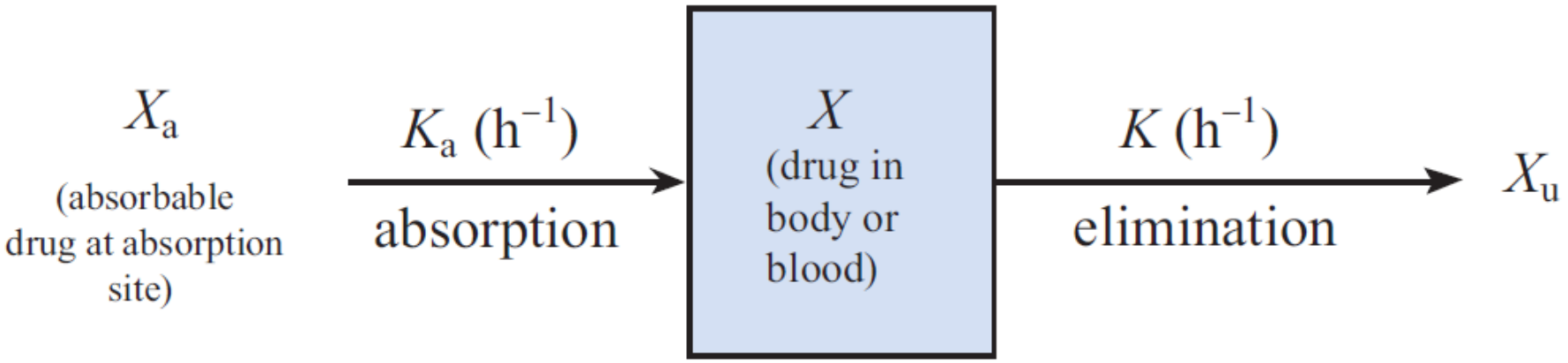
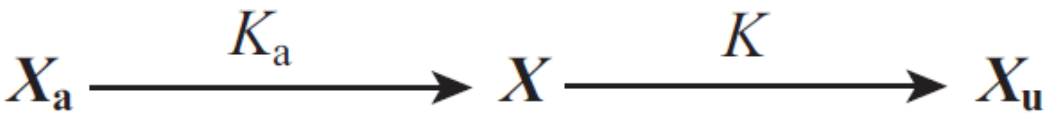
- PK parameters, from C_p Vs time data, following oral administration of drugs, are determined with the following **assumptions**:
  - Drug exhibits the characteristics of one compartment model,
  - Absorption and elimination of a drug follow the first-order process and passive diffusion,
  - Drug is eliminated in unchanged form (i.e. no metabolism occurs),
  - Drug is monitored in the blood.


X_a
(absorbable drug at absorption site)
K_a (h^{-1})
absorption
X
(drug in body or blood)
K (h^{-1})
elimination
X_u

SETUP:


X_a
K_a
X
K
X_u

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- For a drug that enters the body by an apparent first-order absorption process, is eliminated by a first-order process, and distributes in the body according to a one-compartment model, the following differential equation applies:

$$\frac{dX}{dt} = K_a X_a - KX$$

where X and K are as defined previously, K_a is the apparent first order absorption rate constant, and X_a is the amount of drug at the absorption site.

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- Assuming 'F' is the fraction of the oral dose (X_O) that will be absorbed ultimately;
  - Then, the amount of drug available for absorption at t = 0, X_a^O

$$\boldsymbol{X_a^O = FX_O}$$

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- The rate of disappearance of the drug from the absorption site is described by:

$$\frac{dX_a}{dt} = -K_a X_a \qquad \text{or} \qquad X_a = X_a^O e^{-K_a t}$$

- Substituting FX_O for X_a^O

$$X_a = FX_O e^{-K_a t}$$

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- Substituting $FX_O e^{-K_a t}$ for X_a in the differential equation for the amount of the drug in body ($\frac{dX}{dt} = K_a X_a - KX$):

$$\frac{dX}{dt} = K_a F X_O e^{-K_a t} - KX$$

- Integrating this equation:

$$X = \frac{K_a F X_O}{(K_a - K)} (e^{-Kt} - e^{-K_a t})$$

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- Dividing the above equation by V yields:

$$\frac{X}{V} = C = \frac{K_a F X_O}{V(K_a - K)}\left(e^{-Kt} - e^{-K_a t}\right)$$

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Elimination half life ($t_{1/2}$) and elimination rate constant (K)

- For most drugs administered extravascularly in conventional dosage forms, $K_a \gg K$.
- As a result, at some time after administration, the term $e^{-K_a t}$ approaches zero, whereas the term e^{-Kt} is finite,
- Therefore, the eqn. $\left[C = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})\right]$ reduces to

$$C = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt})$$

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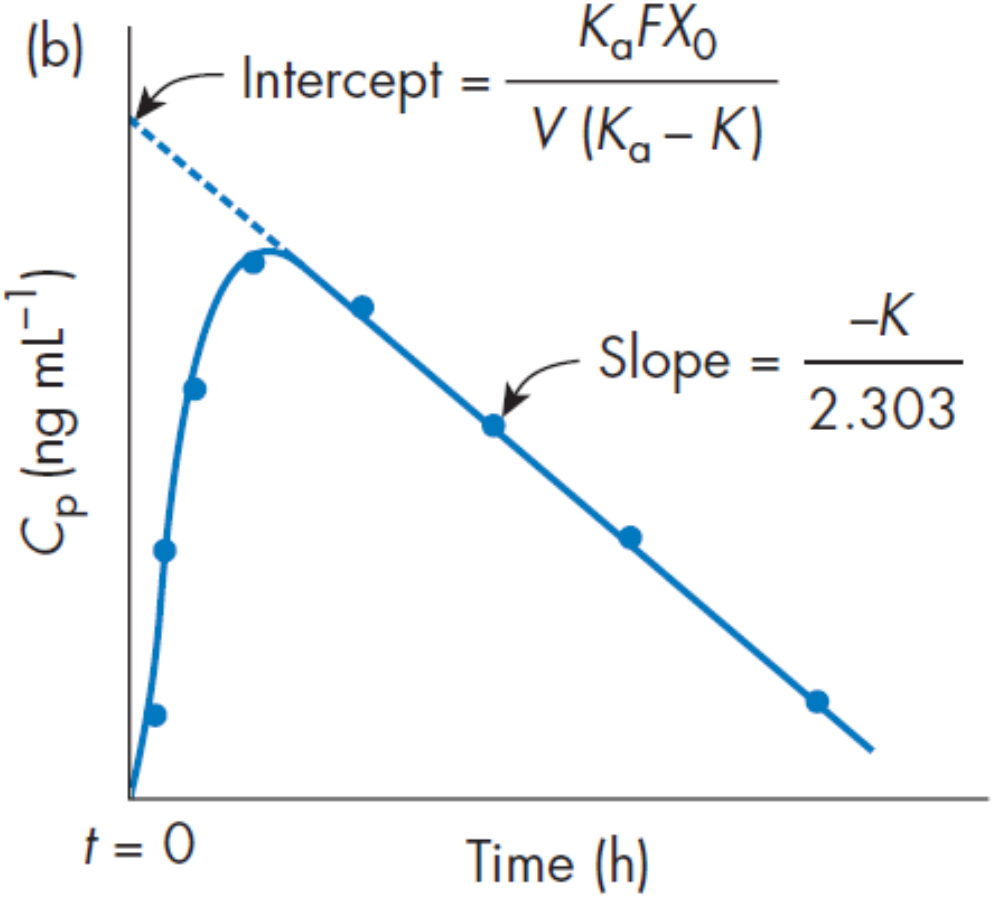
- A plot of the logarithm of drug concentration in plasma versus time yields a biexponential curve, with a terminal linear portion having a slope of $-\frac{K}{2.303}$.

$$\log C = \log\left[\frac{K_a F X_O}{V(K_a - K)}\right] - \frac{Kt}{2.303}$$

- Elimination half-life of the drug is given by $\frac{0.693}{K}$.


(b)
Intercept = $\frac{K_a F X_0}{V (K_a - K)}$
Slope = $\frac{-K}{2.303}$
C_p (ng mL^{-1})
$t = 0$
Time (h)

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Absorption rate constant (K_a)

- The absorption rate constant is determined by a method known as "**method of residuals**"
- The method allows the separation of the monoexponential constituents of a biexponential plot of plasma concentration against time.
- This graphical approach for estimating K_a is useful only if K_a and K rate constants are substantially different.
    - In general, the method works best if $\frac{K_a}{K} \geq 3$.

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- If this is not the case (i.e. if $\frac{K_a}{K} is\ not \geq 3$), the rate constants are best estimated by fitting the concentration-time data to:

$$C = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

with the aid of a *nonlinear least-squares regression* program.

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Method of residuals

- From the equation,

$$C = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

- Assuming that $K_a \gg K$, the term $e^{-K_a t}$ will approach zero, whereas the term e^{-Kt} retains a finite value, then the equation reduces to:

$$C = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt})$$

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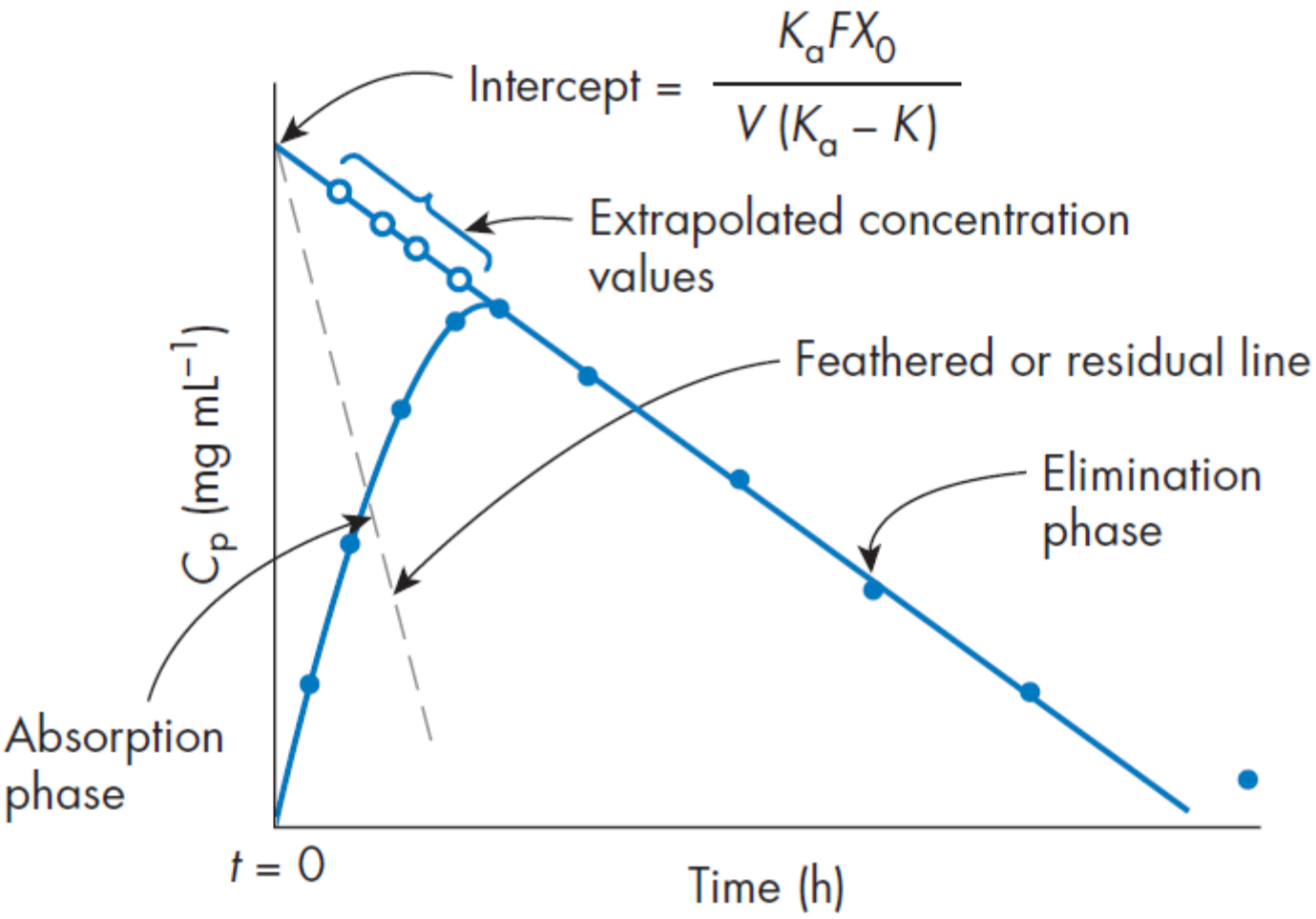
- A plot of the $\log C$ vs. t yields a biexponential curve
  - Extrapolation of the terminal linear phase to time zero will yield an intercept equal to:

$$\log\left[\frac{K_a F X_O}{V(K_a - K)}\right]$$

  - Subtraction of the true plasma concentration values in the absorptive phase from the corresponding concentration values on the extrapolated line yields a **series of residual concentrations**.


Intercept = $\frac{K_a F X_0}{V(K_a - K)}$
Extrapolated concentration values
Feathered or residual line
Elimination phase
Absorption phase
C_p (mg mL^{-1})
$t = 0$
Time (h)

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- These residual values are described by:

$$C_R = C_{extrapolated} - C_{observed}$$

And,

$$C_{extrapolated} = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt})$$

$$C_{observed} = \frac{K_a F X_O}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

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- Therefore,

$$C_R = \frac{K_a F X_O}{V(K_a - K)}\left(e^{-K_a t}\right)$$

- In terms of common logarithms

$$\log C_R = \log\left[\frac{K_a F X_O}{V(K_a - K)}\right] - \frac{K_a t}{2.303}$$

- Then, a plot of $\log C_R$ vs t yield a straight line with a slope of $-\frac{K_a}{2.303}$

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- Some drugs are absorbed very slowly. Other drugs are eliminated from the body very rapidly.

- In either case, absorption may be relatively slow compared to elimination and the absorption rate constant may be smaller than the elimination rate constant.

- In such cases, the slope of the linear segment of the semi log plot of C vs t is equal to $-\frac{K_a}{2.303}$ rather than $-\frac{K}{2.303}$ and the elimination rate constant must be determined by the method of residuals.

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- Note:
  - In the method of residuals, the absorption process is assumed to be of the first order kinetics.
  - This assumption is valid for solutions and rapidly dissolving dosage forms, where the absorption process itself is rate determining.
  - In cases where the release of the drug from the dosage form is rate limiting, the kinetics are often zero order, mixed zero and first order, or even more complex processes.

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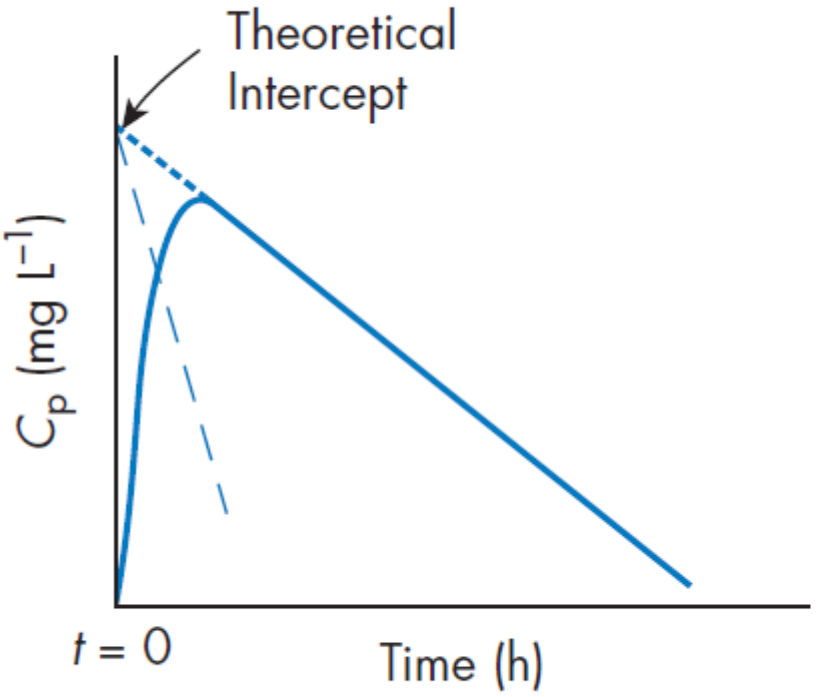
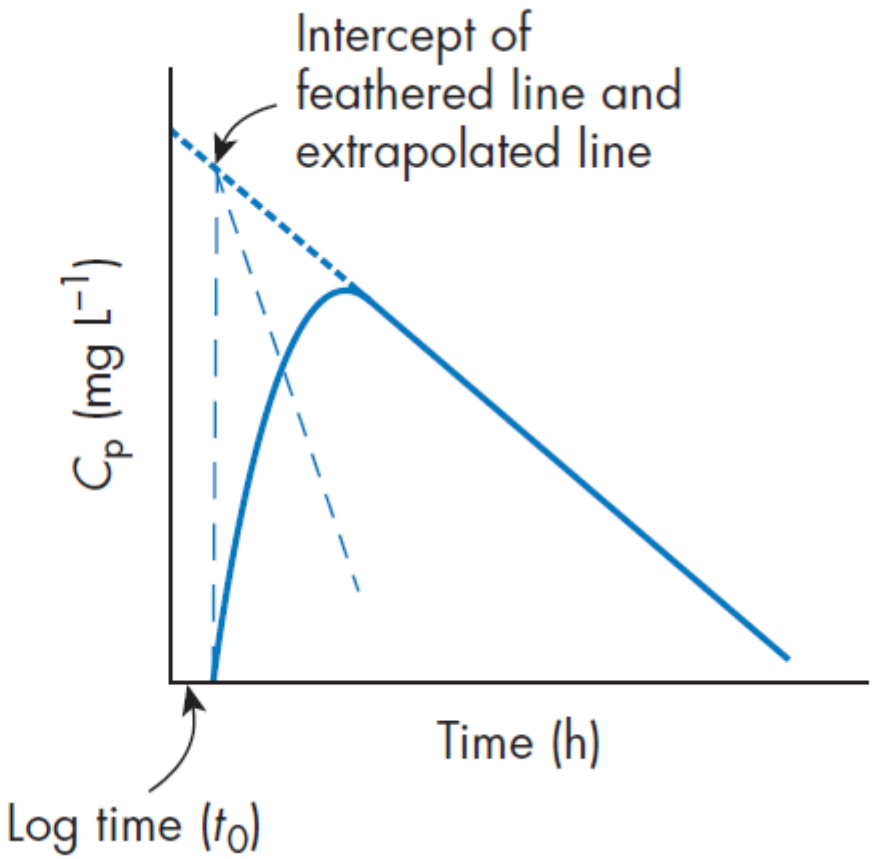
Lag time (t_0)

- The time course of concentration in plasma of certain drugs suggests a time lag between oral administration and the apparent onset of absorption.
- This lag may be the result of delayed release of drugs from the dosage form or of a combination of negligible absorption from the stomach and slow gastric emptying.
- One usually concludes the existence of a 'lag time' if the intersection of the extrapolations of the terminal exponential phase and residual line occurs at a time greater than zero.


Theoretical
Intercept
C_p (mg L^{-1})
$t = 0$
Time (h)


Intercept of
feathered line and
extrapolated line
C_p (mg L^{-1})
Time (h)
Log time (t_0)

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- When a lag is evident, the appropriate equation to describe the time course of drug concentrations in plasma is:

$$C = \frac{K_a F X_O}{V(K_a - K)}\left(e^{-K(t-t_O)} - e^{-K_a(t-t_O)}\right)$$

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Determination of C_{max} and t_{max}

- The peak time (**t_{max}**) is the time at which the body displays the maximum plasma concentration (**C_{max}**).
- It occurs when the rate of absorption is equal to the rate of elimination.
- At the peak time, therefore,

$$K_a(X_a)_{t_{max}} = K(X)_{t_{max}}$$

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- According to the rate of change amount of the drug in body:

$$\frac{dX}{dt} = K_a X_a - KX$$

- At t = t_{max}

$$\frac{dX}{dt} = K_a (X_a)_{t_{max}} - K(X)_{t_{max}} = 0$$

$$K_a (X_a)_{t_{max}} = K(X)_{t_{max}}$$

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- The amount drug in the body at time t is given by:

$$(X)_t = \frac{K_a F X_O}{(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

- And, the amount to be absorbed:

$$(X_a)_t = F X_O e^{-K_a t}$$

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- Substituting t_{max} for t in the above equations

$$(X)_{t_{max}} = \frac{K_a F X_O}{(K_a - K)} (e^{-K t_{max}} - e^{-K_a t_{max}})$$

- And,

$$(X_a)_{t_{max}} = F X_O e^{-K_a t_{max}}$$

- Then (substituting, rearranging and simplifying), we get

$$K_a e^{-K_a t_{max}} = K e^{-K t_{max}}$$

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- Rearranging the above equation:

$$\frac{K_a}{K} = \frac{e^{-Kt_{max}}}{e^{-K_a t_{max}}}$$

- Taking the logarithm of both sides and solving for t_{max} yields:

$$t_{max} = \frac{2.303}{K_a - K} \log \frac{K_a}{K}$$

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- Maximum plasma concentration is described by substituting t_{max} for t in:

$$C_{max} = \frac{K_a F X_O}{V(K_a - K)} (e^{-K t_{max}} - e^{-K_a t_{max}})$$

- But from $\frac{K_a}{K} = \frac{e^{-K t_{max}}}{e^{-K_a t_{max}}}$,

$$e^{-K_a t_{max}} = \frac{K}{K_a} e^{-K t_{max}}$$

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- Therefore,

$$C_{max} = \frac{K_a F X_O}{V(K_a - K)} \frac{K_a - K}{K_a} e^{-K t_{max}}$$

- The above equation can be simplified to:

$$C_{max} = \frac{F X_O}{V} e^{-K t_{max}}$$

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Urinary Excretion Data

- Read